EXHIBIT "A"

MECHANISMS OF CELL TRANSFORMATION BY DNA TUMOR VIRUSES

Diversity of DNA Tumor Viruses and Modes of Action of Their Oncogenes

The DNA tumor viruses are a biologically heterogeneous group, distributed among six major families (see Table 1). The degree to which the relationships of these viruses to experimental or naturally occurring cancers are established and understood vary greatly from virus to virus. The polyomaviruses and adenoviruses are recognized as tumor viruses only in experimental systems. Because of their size and ease of manipulation, these viruses are among the best understood in terms of their mechanisms of action in cell transformation. Viruses of the other four groups have been implicated in naturally occurring cancers, both benign and malignant, in various mammalian species, including man. Of these, the papilloma viruses are perhaps the best understood from the standpoints of molecular biology and clinical relevance. Viruses of the remaining groups—hepadna, herpes, and pox—have been implicated in naturally occurring cancers largely through seroepidemiological findings. Experimental studies with viruses of these groups have uncovered basic information concerning their genetic and biological properties (see the respective chapters in this volume). However, definitive information concerning specific viral oncogenes and mechanisms of action in cell transformation is lacking for these viruses.

Table 4 lists the genes of the polyomaviruses, adenoviruses, and papillomaviruses that are known to play a role in cell transformation. Like oncogenes of retroviruses whose actions in cell transformation they resemble, these oncogenes encode proteins that reside in different compartments of the cell and encompass a range of actions similar to elements of a signal transduction pathway. Thus, the middle T protein of the mouse polyomavirus and the product of the E-5 open-reading frame of the fibropapilloma virus BPV-1 reside in membrane fractions of the cell, as does a small subfraction of the SV40 large T protein. Middle T is known to regulate phosphorylation reactions at the plasma membrane through interactions with specific cellular components. The small T proteins of the polyomaviruses, and perhaps also the E7 papilloma viral gene product, are soluble proteins that may act in both the cytoplasm and the nucleus to elicit parts of the transformed cell phenotype. Most of the DNA tumor viral oncogenes appear to act primarily in the nucleus. These include the products of the adenovirus transforming genes E1A and E1B, the large T proteins of the polyomaviruses, and the E-6 and E-7 gene products of the papillomaviruses. These proteins act in multiple ways to alter patterns of gene expression and regulation of cell growth. In every case, these DNA viral oncogenes represent "early" viral functions having dual roles in virus growth and cell transformation.

TABLE 4. *Transforming gene products of DNA tumor viruses*

Viruses	Proteins	Localization/ function[a]
Polyomaviruses		
Mouse polyoma	Large T antigen	N/D
	Middle T antigen	M/S
	Small T antigen	C,N/?
SV40	Large T antigen	N (m,c)/D
	Small T antigen	C,N/?
Adenoviruses	E1A (289 aa; 243 aa)	N/D
	E1B (55 kd; 19kd)	N (m)?
Papillomaviruses	E5	M/S
	E6	N (m,c)/D
	E7	N (m,c)/D

[a] Localization: N, nuclear; M, membrane(s); C, cytoplasm. Uppercase letters indicate major site(s) of localization, and lowercase letters indicate minor site(s) of localization. Function: D, involved directly or indirectly in transcription and/or replication of DNA; S, involved in some aspect of signaling from membrane(s). See text for discussion.

Identification of Viral Oncogenes Based on Virus Growth

The actions of DNA tumor virus genes in cell transformation arise as consequences of particular strategies employed by the virus to regulate its own functions and to condition the cell for efficient virus replication. Unlike retroviral oncogenes, which derive from the cell and play no role in virus replication, oncogenes of the DNA viruses perform essential functions in the virus growth cycle. As true viral genes, they have no strict homologues or direct ancestors among normal cellular genes of the host. For the polyomaviruses and adenoviruses in particular, it has been largely through their normal functions in virus growth that the viral oncogenes have been identified and characterized. These viruses interact with target cells in one of two mutually exclusive ways: (i) productive infection, in which the virus carries out its complete growth cycle and kills the host cell, or (ii) nonproductive infection, in which the virus transforms the cell without completing its growth cycle or producing progeny virus. In the latter interaction, the viral genome usually becomes integrated and continues to express only early gene functions.

Virus mutants that are defective in cell transformation have provided important tools for identifying